PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 35/34, 35/32, 31/715, 38/00 — A1

(11) International Publication Number: **WO 98/26789**

(43) International Publication Date: 25 June 1998 (25.06.98)

(21) International Application Number: PCT/US97/23406

(22) International Filing Date: 18 December 1997 (18.12.97)

(30) Priority Data:
08/769,596 18 December 1996 (18.12.96) US

(71) Applicant: CONSOLIDATED CHEMICALS, INC. [US/US]; 3224 South Kingshighway, St. Louis, MO 63139 (US).

(72) Inventors: MURLEY, Jack, C.; 112 Sunnyside Lane, O'Fallon, IL 62269 (US). BRERETON, John, C.; 770 Straub Road, Chesterfield, MO 63017 (US).

(74) Agent: DENK, Paul, M.; Suite 170, 763 South New Ballas Road, St. Louis, MO 63141 (US).

(81) Designated States: AU, BR, CA, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.
With amended claims.

(54) Title: MICROCLYSMIC GEL FOR TREATMENT OF TISSUE TRAUMA AND BURNS

(57) Abstract

A therapeutic wound gel is provided which will enhance healing of the wound and reduce swelling and elasticity of the skin. Humatrix is bacteriostatic protectant with no bacteriocidal activity. The gel consists essentially of by weight percent, about 88–97 % water, about 0.4–0.6 % carbomer, about 1.2–7.8 % propylene glycol, about 0.6–1.3 % glycerin, about 0.5 % DMDM Hydantoin, about 0–.8 % citric acid, about 0.1 % chondroitin sulfate and animal protein, and about 0–.6 % triethanolamine. The gel is formed in three phases which are combined together, the first phase consisting essentially of about 88–99 % of the water of the gel, the carbomer, the propylene glycol and the glycerin; the second phase consisting essentially of the remaining water, the DMDM Hydantoin, and the citric acid if needed; and the third phase consisting essentially of the chodroitin sulfate and animal protein and the triethanolamine, if needed.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

MICROCLYSMIC GEL FOR TREATMENT OF TISSUE TRAUMA AND BURNS

Background of the Application

This invention relates to gels used to treat tissues, and in particular to a gel which stimulates wound healing in chronic wound, 1st degree, 2nd degree, and 3rd degree burns.

Major tissue trauma requires a lengthy time to heal. If the trauma is not properly treated or managed, the wound can suffer from dehydration, hyperthermia and consequent swelling, hyper-contracture, hyper-granulation, and scarring. These are all obstacles to proper healing and significantly affect health care costs.

Summary of the Invention

One object of the present invention is to provide a gel which will enhance the healing of tissue wounds via bio-chemistry..

Another object is to provide such a gel which will provide rapid heat reduction for the wound bed or damaged tissue.

Another object is to provide such a gel which will reduce hyper-granulation, hyper-contracture, and scarring.

Another object is to provide such a gel which will enhance the extensibility and flexibility of human skin.

These and other objects will become apparent to those skilled in the art in light of the following disclosure and accompanying drawings.

In accordance with the invention, generally stated, a therapeutic wound gel is provided which will enhance healing of the wound and reduce swelling and improve elasticity of the skin. The gel consists essentially of by weight percentage about 88-97% water, about 0.4-0.6% carbomer, about 1.2-7.8% propylene glycol, about 0.6-1.3% glycerin, about 0.5% DMDM Hydantoin, about 0-.8% citric acid, about 0.1% chondroitin sulfate and animal protein, and about 0-.6% triethanolamine. The gel is formed in three phases which are combined together, the first phase consisting essentially of about 80-99% of the water of the gel, the carbomer, the propylene glycol and the glycerin; the second phase consisting essentially of the remaining water, the DMDM Hydantoin, and the citric acid if needed; and the third phase consisting essentially of the chodroitin sulfate and collagen and the triethanolamine, if needed.

Description of the Preferred Embodiment

The gel of the present invention is made of H_2O, carbomer, propylene glycol, glycerin, DMDM Hydantoin, citric acid, cromoist CS (a combination of chondroitin sulfate and hydrolized animal protein) and triethanolamine. Carbomer is a homopolymer of acrylic acid cross linked with an allyl ether of pentaery thritol or an allyl ether of sherose, available from Goodrich and which forms stable emulsions of oils in water. The propylene glycol is

provided to slow down the transepidermal loss of water, and thus helps to keep the wound moist. The glycerin, when used in low concentrations, as is done herein, acts to attract moisture from the air onto the skin surface. This also aids in keeping the wound moist. DMDM Hydantoin is 1,3-dimethylol available from Lonza and is provided to long term stability and preservation. Cromoist CS is a combination of chondroitin sulfate and hydrolized animal protein, available from Croda. The Cromoist CS is provided to moisturize the wound and to reduce transepidermal water loss at low relative humidities. The action of the Cromoist CS increases the synergism of the propylene glycol, glycerine and DmDM Hydantoin render the gel bacteriostatic but not bacteriocidal. This product is designed to be used in conjunction with Techni-Care®, Clinical Care®, and Care-Creme®,in the therapeutic treatment and the extensibility and flexibility of the skin. The chondroitin sulfate in the Cromoist CS is a glycosaminoglycan which acts as a flexible connecting matrix and serves to promote and accelerate regeneration of the tissue by replicating the natural fibro-connective template and stimulating fibroblast activity. That is, it creates a precursor to collagen formation. The addition of the glycosaminglycans thus helps to increase the extensibility and flexibility of the skin while providing pain reduction by reducing the heat and swelling of the wound.

The gel is produced in a three phase process, the compositions of which are as follows:

Component	Purpose	Amount (gm)
Phase A		
Water	diluent	90.70 ± 10.0
Carbomer	humectant	0.5 ± 0.2
Propylene Glycol	humectant	5.0 ± 4.0
Glycerin	humectant	1.0 ± 0.5
Phase B		
Water (UV sterilized)	diluent	1.0 ± 0.5
DMDM Hydantoin		0.5 ± 0.1
Citric acid	chelating agent	0.70 ± 0.25
Phase C		
Cromoist (Chondroitin sulfate and animal protein)	glycosaminoglycan	0.10 ± 0.05
Triethanolamine	pH adjuster	0.50 ± 0.25

The gel is made as follows. Sterile H_2O and Carbomer of phase A are initially mixed together under high shear for preferably 1-2 minutes. The propylene glycol and glycerin are added next in order, again under high shear mixing. The components of Phase B are mixed together and then, when completely dissolved, are added to Phase A and mixed therewith to produce an homogenous mixture. The citric acid is added only if necessary to adjust the pH to a pH of between 6.5 and 7.5. The Cromoist CS, of Phase C is then added slowly to the mixture of Phase A and B. When the Cromoist has been added, the triethanolamine is added to adjust the pH of the mixture to a final pH of about 7.0. Mixing is then continued until a clear gel is obtained.

In use, once a wound has been thoroughly cleaned with an antimicrobial cleanser, the gel of the present invention is applied to the wound. The gel is applied in a layer that is 4mm to 6mm thick. The wound is then covered with a non-occlusive dressing. To maintain a moist wound

environment, the gel is reapplied each time the dressing is changed or twice daily.

Application of the gel has been found to reduce the surface temperature of a would by 12°C to 18° C in approximately three minutes. This prompt cooling reduces hyperthermia and associated tissue swelling. The temperature reduction capacity is essential to pain management attributes of this formulation and for it's use in 3rd degree burns.

As variations within the scope of the appended claims may be apparent to those skilled in the art, the foregoing description is set forth only for illustrative purposes and is not meant to be limiting.

CLAIMS:

1. A therapeutic wound gel comprised essentially of water, carbomer, propylene glycol, glycerin, DMdM Hydantoin, chondroitin sulfate, and animal protein.

2. The therapeutic would gel of Claim 1 further including citric acid and triethanolamine to adjust pH of the gel to about 7.0.

3. The therapeutic wound gel of Claim 2wherein the gel consists generally of, by weight percent, about 88-97% water, about 0.4-0.6% carbomer, about 1.2-7.8% propylene glycol, about 0.6-1.3% glycerin, about 0.5% DMDM Hydantoin, about 0-.8% citric acid, about 0.1% chondroitin sulfate and animal protein, and about 0-.6% triethanolamine.

4. The therapeutic wound gel of Claim 3 wherein the citric acid comprises about 0.5-0.95% of the gel and the triethanolamine comprises about 0.3-0.75% of the gel.

5. The therapeutic would gel of Claim 4 wherein the gel is formed in three phases which are combined together, the first phase consisting essentially of about 80-99% of the water of the gel, the carbomer, the propylene glycol and the glycerin; the second phase consisting essentially of the remaining water, the DMDM Hydantoin, and the citric acid if needed; and the third phase consisting essentially of the chondroitin sulfate and animal protein and the triethanolamine, if needed.

AMENDED CLAIMS

[received by the International Bureau on 12 May 1998 (12.05.98); new claims 6 and 7 added; remaining claims unchanged (2 pages)]

1. A therapeutic wound gel comprised essentially of water, carbomer, propylene glycol, glycerin, DMdM Hydantoin, chondroitin sulfate, and animal protein.

2. The therapeutic would gel of Claim 1 further including citric acid and triethanolamine to adjust pH of the gel to about 7.0.

3. The therapeutic wound gel of Claim 2wherein the gel consists generally of, by weight percent, about 88-97% water, about 0.4-0.6% carbomer, about 1.2-7.8% propylene glycol, about 0.6-1.3% glycerin, about 0.5% DMDM Hydantoin, about 0-.8% citric acid, about 0.1% chondroitin sulfate and animal protein, and about 0-.6% triethanolamine.

4. The therapeutic wound gel of Claim 3 wherein the citric acid comprises about 0.5-0.95% of the gel and the triethanolamine comprises about 0.3-0.75% of the gel.

5. The therapeutic would gel of Claim 4 wherein the gel is formed in three phases which are combined together, the first phase consisting essentially of about 80-99% of the water of the gel, the carbomer, the propylene glycol and the glycerin; the second phase consisting essentially of the remaining water, the DMDM Hydantoin, and the citric acid if needed; and the third phase consisting essentially of the chondroitin sulfate and animal protein and the triethanolamine, if needed.

6. The therapeutic wound gel of Claim 1 wherein the gel, when applied to a wound in a pharmaceutically effective amount, reduces the surface temperature of the wound by about 12°C-18°C in about three minutes.

7. The therapeutic wound gel of claim 6 wherein the wound gel comprises by weight percent, about 88-97% water, about 0.4-0.6% carbomer, about 1.2-7.8% propylene glycol, about 0.6-1.3% glycerin, about 0.5% DMDM Hydantoin, about 0-0.95% citric acid, about 0.1% chondroitin sulfate and animal protein, and about 0-0.75% triethanolamine.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/23406

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 35/34, 35/32, 31/715, 38/00
US CL :424/548, 549; 514/54, 21
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/548, 549; 514/54, 21

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, USPATFULL, MEDLINE, HCAPLUS, EMBASE, BIOSIS- CLAIMED INGREDIENTS IN COMPOSITIONS TOGETHER, ESPECIALLY FOR THE TREATMENT OF SKIN DISORDERS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,519,046 A (NODA et al.) 21 May 1996, see entire document.	1-5
Y	US 5,470,911 A (RHEE et al.) 28 November 1995, see entire document.	1-5
Y	Database HCAPLUS on STN, American Chemical Society, FARINA ET AL., "Method for preparing low free formaldehyde methyol-hydantoins and compositions thereof", AN 1994:245102, EP 571903 A1, abstract.	1-5

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 24 FEBRUARY 1998	Date of mailing of the international search report 20 MAR 1998
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer M. MOEZIE Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*